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Radiolocalization of the Sentinel Lymph Node in Merkel Cell Carcinoma: A Clinical Analysis of Seven Cases

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Merkel cell carcinoma (MCC) is a rare cutaneous skin lesion with a variable but often aggressive clinical course. Patient survival correlates with nodal status and the presence of distant metastases. The histologic status of the sentinel lymph node consistently correlates with the incidence of regional lymphatic metastases in other dermal malignancies. The technique of radiolocalization and surgical resection of the sentinel lymph node using an intraoperative gamma probe is used to guide clinical management in these patients. We report on seven cases of MCC managed utilizing this technique. Four patients had negative sentinel nodes and no other nodal disease at completion lymphadenectomy (n = 2) or clinical follow-up (n = 2) and currently remain disease free. Two patients had a positive sentinel node but no other positive lymph nodes at completion lymphadenectomy; one of them developed regional recurrence. One patient with a positive sentinel node and six additional positive nodes developed extensive nodal disease and systemic recurrence during radiotherapy and expired of MCC. Our results suggest that the sentinel node was identified and removed successfully using radiolocalization making this technique useful in the staging and therapy of patients with MCC.
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KEY WORDS: **Merkel cell carcinoma; neuroendocrine carcinoma; sentinel node; gamma probe; radiolocalization; lymph node; staging**

INTRODUCTION

Merkel cell carcinoma (MCC) is a rare cutaneous skin lesion distinguished by the presence of neurosecretory granules commonly found in the Merkel cell. The Merkel cell has not been clearly implicated in the histogenesis of the tumor, and there is evidence that this tumor may arise from a pluripotential cell in the epidermis [1]. It occurs most often in elderly patients on sun-exposed areas, most frequently the head and neck. The clinical course is highly variable, but a large proportion of these tumors have exceedingly aggressive characteristics [2]. Nodal disease is found at presentation in 15–25% of patients and develops during the course of the disease in 50–55% [1,3–5]. Local failure following surgery occurs in 26–45% of patients at a median interval of 8 months [1,3–5]. Survival is not statistically correlated with local recurrence but is negatively affected by positive nodes or distant metastases [1,3,6]. Shaw and Rumball have demonstrated that nodal status is predictive, with 67% mortality of node-positive patients versus 23% of patients without regional failure [6]. Distant metastases have been found to occur within 2 years [1,2,7] and may develop concurrently with nodal spread [1].

Recent studies have demonstrated that the histologic status of the sentinel lymph node consistently correlates with the incidence of regional lymphatic metastases in patients with breast cancer and melanoma [8–10]. The

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TABLE I. Summary of Seven Cases of Merkel Cell Carcinoma Undergoing Radioloclization and Sentinel Node Resection*

Case no.	Sex	Age (yr)	Location of primary tumor	Sentinel node status	Other nodal disease	Condition at follow-up (mos)	Other tumors
1	F	77	LUE	Negative	0/18	Disease free (16)	Melanoma
2	F	70	LUE	Positive	0/19	Local recurrence (4)	CLL, uterine adenocarcinoma
3	M	63	RLE	Positive	5/7	Systemic recurrence (6)	CLL
4	F	83	RLE	Negative	0/7	Disease free (8)	None
5	F	78	RUE	Positive	0/20	Disease free (11)	None
6	M	75	RLE	Negative (no RLND)	0/2	Disease free (4)	None
7	M	79	LLE	Negative (no RLND)	0/2	Disease free (6)	CLL

*LUE, left upper extremity; RUE, right upper extremity; LLE, left lower extremity; RLE, right lower extremity; RLND, regional lymph node dissection; CLL, chronic lymphocytic leukemia.

technique of radiolocalization and surgical resection of the sentinel lymph node using an intraoperative gamma probe is well described in the management of breast cancer and melanoma [8,11]. MCC is similar in natural history to melanoma [1,6], making sentinel lymph node localization a reasonable approach. The success of this technique requires that the status of the resected node be predictive of overall nodal involvement. This relationship is not known for MCC, but the similarities to melanoma warrant investigation. We report on seven cases of MCC managed utilizing gamma probe-guided resection of the sentinel lymph node.

MATERIALS AND METHODS

Seven patients underwent lymphatic localization using radiocolloid prior to excision of biopsy-proven MCC. Technetium sulfur colloid, 0.4–0.5 μCi, (CIS-US, Bedford, MA), was injected circumferentially into the dermis around the biopsy site or tumor. Gamma camera images were obtained in 4/7 patients.

A gamma detector (C-Trak, CareWise Medical, Morgan Hill, CA) was used to identify the ''hot spot'' corresponding to the underlying radioactive node(s) in the regional drainage area. This location was marked on the skin and dissection carried down to remove the node. Counts of the radioactive nodes were obtained ex vivo. Following removal of the sentinel node the probe was placed into the resection bed to verify that all radioactive nodes had been removed. A standard regional lymphadenectomy was then performed in five of seven cases.

RESULTS

All cases are presented in Table I. Brief narrative descriptions follow. All sentinel lymph nodes were successfully located and excised. Four patients had negative sentinel nodes and no other nodal disease at completion lymphadenectomy ($n = 2$) or clinical follow-up ($n = 2$) and currently remain disease free. Two patients had a positive sentinel node but no other positive lymph nodes at completion lymphadenectomy. One of these had a local recurrence at 4 months that was excised and had no clinical evidence of MCC at the time of her death from uterine cancer. The other is disease free. One patient with a positive sentinel node had six additional positive nodes at completion lymphadenectomy. This patient developed extensive nodal disease during radiotherapy and ultimately expired due to systemic complications.

CASE REPORTS

Case 1

A 77-year-old white woman presented following wide excision of an MCC at her left wrist. She had a history of excision of melanoma from her left elbow several years previously and had no further manifestations of this disease. She underwent complete axillary lymphadenectomy following radiolocalization and resection of the sentinel node. Seventeen other nodes were resected. The final pathology revealed 18 nodes negative for tumor. She received adjuvant radiotherapy to the wrist and is currently disease free.

Case 2

A 70-year-old white woman with a past medical history of chronic lymphocytic leukemia (CLL) and uterine adenocarcinoma presented with an enlarging mass on the posterior aspect of her left arm. Local excision and pathologic evaluation demonstrated MCC. She underwent sentinel node resection followed by wide excision of the previous biopsy site and axillary lymphadenectomy. The sentinel node was positive for tumor. Nineteen additional nodes were negative.

She developed a local recurrence 5 months later. This was excised with negative surgical margins, and she received adjuvant radiotherapy. There was no evidence of recurrent MCC at the time of her death from metastatic uterine adenocarcinoma 6 months later.

Case 3

A 63-year-old white man with a 10-year history of CLL presented in March of 1994 with a 4-month history of a right thigh lesion that had been increasing in size and tenderness. Excisional biopsy demonstrated MCC. He underwent radiolocalization of the sentinel node fol-

lowed by wide excision, split-thickness skin grafting, and a right superficial inguinal node dissection. Six of seven nodes, including the sentinel node, were positive for tumor. He received nodal radiotherapy but was unable to tolerate full pelvic irradiation.

Six months postoperatively the patient developed extensive inguinal recurrence. Nine months postoperatively he developed a recurrence on his left thigh as well as radiographic evidence of pelvic and mesenteric MCC. He was given radiotherapy and chemotherapy, but his disease continued to progress. He died of systemic complications of MCC at 11 months follow-up.

Case 4

An 83-year-old white woman presented with an enlarging lesion on her right forearm. Excisional biopsy demonstrated MCC. The patient underwent wide local excision and axillary lymph node dissection. One sentinel node was identified and was histologically negative for tumor. Seven additional nodes were all negative for tumor. She remains disease free at 8 months follow-up.

Case 5

A 78-year-old white woman presented with a left upper extremity nodule confirmed as MCC by excisional biopsy. She underwent sentinel node radiolocalization, wide excision of the previous biopsy site, and a complete axillary lymphadenectomy. Three sentinel nodes were resected. One sentinel node was positive for tumor. The additional 20 nodes were negative for tumor. At 11 months follow-up she remains disease free.

Case 6

A 79-year-old man presented with a 2–3 cm lesion on the left thigh that had become increasingly tender. Excisional biopsy revealed MCC. He underwent radiolocalization of two sentinel nodes and wide excision of his primary lesion. Both sentinel nodes were negative for tumor and he did not undergo a complete regional lymphadenectomy. He is disease free at 4 months follow-up.

Case 7

A 75-year-old man presented with a 12-month history of a nodule on his right buttock that had been gradually increasing in size. He had a history of CLL several years previously. Excisional biopsy revealed MCC. He underwent resection of two sentinel nodes identified by radiolocalization and wide excision of his primary tumor. He did not have an inguinal lymphadenectomy. Pathology revealed two nodes negative for tumor. He is currently disease free at 6 months follow-up.

DISCUSSION

These seven patients illustrate several common features of MCC. MCC has been described in association with other tumors (including CLL) that occurred in three of our patients. Immune compromise in these patients has been implicated [1]. MCC occurred on an extremity in all of our patients, with one case in the buttock region. All patients presented with enlarging dermal nodules, the most common presentation for MCC [3]. Three patients of seven (43%) presented with occult nodal disease.

Adjuvant radiotherapy is used in addition to surgery in patients with tumor approximating the surgical margin, vascular involvement on histology, or nodal metastasis [4,12]. However, no difference has been found between adjuvant therapy and aggressive surgery alone in the treatment of node-negative patients in the few retrospective studies that exist [3]. Adjuvant therapy may play a role in patients with local failure or extensive nodal disease [3,4,12]. Two of our patients received radiotherapy under these circumstances, one for a local recurrence following re-excision and the other for extensive regional disease.

Nodal metastases are common in MCC and are predictive of outcome [1,3]. Five-year survival rates for patients with nodal disease are less than 50% versus 88% survival in the absence of regional metastases [3,5]. Tumor site, size, surgical margin, and proximity of the lesion relative to the regional node basin have not been found to be predictive of nodal disease [3]. These characteristics support the role of tumor staging by lymph node sampling to provide prognostic information to the patient as well as to select patients for regional lymphadenectomy and adjuvant therapy.

Selective lymphadenectomy is based on the presence of disease in the sentinel lymph nodes and offers the opportunity to select patients who require regional lymphadenectomy, thereby avoiding the morbidity of a procedure in the 75% of MCC patients who present without nodal disease. A consistent relationship between the histologic status of the sentinel node and the presence or absence of regional disease has been demonstrated for breast cancer and melanoma, and selective lymphadenectomy is being used in these diseases [8,10,11]. Melanoma and MCC share many characteristics [3,6]. Similar nodal drainage patterns in MCC should allow reliable identification of node-positive patients with the gamma probe guided-surgery.

The seven cases of MCC presented here suggest that sentinel lymph node localization may predict regional nodal status in this disease. Two of three patients with positive sentinel nodes and no additional positive nodes developed recurrent disease. In addition, none of the four patients with negative sentinel nodes have had recurrent nodal disease.

Limitations of our study include a small sample size and relatively short follow-up times. Small sample size is a persistent problem when studying MCC due to its varied forms and relative scarcity in the population. Follow-up on four of five of our disease-free patients is currently at or beyond the 7–10 months quoted as the most frequent time to recurrence. Nonetheless, the technique itself requires a minimal amount of intraoperative technology and technical education and provides a minimally invasive staging technique.

CONCLUSIONS

These results suggest that the sentinel node is predictive of regional nodal status in patients with MCC. Resection of the sentinel node could provide accurate staging information to the surgeon in order to provide prognostic information and guide clinical management. Furthermore investigation in a larger, multicenter series will further define its role in the disease.

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